REMARKS

Claims 1-5, 7-10 and 20 are currently pending in the application. Claims 11-19 and 21 were previously withdrawn. Claims 1 and 2 have been previously amended. The rejection of claims 1-6 under 35 U.S.C. § 102(a) as being anticipated by Zabonina et al. is withdrawn. Paragraph [0026] of the specification has been amended to insert the appropriate SEQ ID Nos. for Figure 11. Support for the instant amendments is found throughout the specification as filed and the original claims. Claims 1-3, 5, 6 and 10 have been currently amended in this response. Support for these amendments is found in the specification as filed. These amendments introduce no new matter. By the amendments, Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

The Examiner states that claims 1, 2, 9 and 10 and their dependent claims have an effective priority date of 8/15/2003 and that the office also establishes effective filing date of 8/15/2003 for claims 8 and 20 in view of an intervened reference applied in the office action. Office Action, p. 2. Applicants respectfully disagree.

The present application claims priority to U.S. Provisional Patent Application Serial Number 60/414,550, filed August 15, 2003, and is a continuation-in-part to U.S. Patent Application Serial Number 10/047,710, filed January 15, 2002, which claims priority to U.S. Provisional Patent Application Serial Number 60/269,133, filed February 15th, 2001.

Support for the subject claims can be found throughout U.S. Provisional Patent Application Serial Number 60/269,133. For example, see Figures 1-15. Support for the subject claims can also be found throughout U.S. Patent Application Serial Number 10/047,710. For example, see Figures 1-8, Examples 1-16, and paragraphs [028]–[031] and [062].

I. Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-10 and 20 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite in allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Office Action, p. 3. The Examiner

argues that claims 1-10 and 20 are indefinite because the term "an effective amount" in claim 1 is not clear. Office Action, p. 3. Applicants respectfully traverse.

While not acquiescing to propriety of the grounds of this rejection, and soley in an effort to expedite prosecution, claim 1 has been amended to delete the objectionable language "an effective amount of" and the language "or a variant or derivative thereof" and to add the language "a pharmaceutical composition comprising a cupredoxin." Applicants reserve the right to file divisional and continuing applications with claims addressing the deleted subject matter. Applicants maintain that the claims as amended are fully supported by the specification.

The language "a pharmaceutical composition comprising a cupredoxin" is supported in paragraph [011] of the specification, which teaches that "[t]he cytotoxic factor, or a variant or derivative thereof, can be incorporated into a pharmaceutical composition for use in the prevention and treatment of conditions related to abnormal cell proliferation."
Hence, Applicants respectfully request reconsideration and withdrawal of the present rejection of claims 1-10 and 20 under 35 U.S.C. § 112, second paragraph.

II. Rejection under 35 U.S.C. § 112, first paragraph

Written Description

Claims 1-10 and 20 remain rejected under 35 U.S.C. § 112, first paragraph, "as failing to comply with the written description requirement." Office Action, p. 4-7. Applicants respectfully traverse.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003). An applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which make it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc. that set forth the claimed invention". *Regents of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1666 (Fed. Cir. 1997). The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time

of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language. *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983).

While not acquiescing to propriety of this rejection, and solely in an effort to expedite prosecution, claims 1 and 2 have been amended to delete the language "or a functional variant or derivative thereof" Applicants reserve the right to file divisional and continuing applications with claims addressing the deleted subject matter. Applicants maintain that the claims as amended are fully supported by the specification.

While not acquiescing to propriety of the grounds of this rejection, claim 5 has been amended to delete the language "or an amino acid sequence having at least 90% sequence identity with SEQ ID NO: 1" and to add the language "a mutant azurin or a truncated azurin." Claim 6 has been amended to remove "is an azurin comprising the amino acid sequence of SEQ ID NO:1, or an amino acid sequence having at least 90% sequence identity with SEQ ID NO:1 and wherein the cupredoxin." Claim 10 has been amended to delete the language "or an amino acid sequence having at least 90% sequence identity with SEQ ID NO: 2" and to add the language "a mutant plastocyanin or a truncated plastocyanin." Applicants reserve the right to file divisional and continuing applications with claims addressing the deleted subject matter. Applicants maintain that the claims as amended are fully supported by the specification.

Support for truncated and mutant cupredoxins is provided throughout the present application, e g., at paragraphs [014], [026], [027], [028], [078], [083-086], [0112-0120] and Examples 19-21 and Figures 11-13. See also U. S. Patent No. 7,089,105 (Ser. No. 10/047,710, filed January 15, 2002 from which the present application claims priority) which is coextensive with the present application and specifically discloses and claims truncated cupredoxins.As taught in paragraph [0112], mutations and/or truncations of cytotoxic factors can produce cytotoxic agents of varying compositions also demonstrating functional activity. Paragraphs [0112 -00120] teach how to develop a truncated or mutant cupredoxin from azurin or plastocyanin. Moreover, Examples 19-21 and Figures 11-13 teach that such cupredoxins do induce the apoptosis rate and cell cytotoxicity.

The Examiner argues that the skilled artisan cannot envision the detailed chemical structure(s) and functional attributes(s) of the encompassed genus of variants or derivatives of azurin and plastocyanin used in the method, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity of simplicity of the method of

isolation. Office Action, p. 5. However, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568. In the present application, the specification teaches identifying characteristics, chemical similarities such as being electron transfer proteins and structural similarities of numerous cupredoxin compounds, including azurin and plastocyanin. See paragraphs [070]-[075]. Hence, the present application teaches, through a sufficient description a representative number of species sufficient to show the applicant was in possession of the claimed genus.

The Examiner further argues that one "cannot envision the detailed chemical structure(s) and functional attribute(s) of the encompassed genus of variants . . . of azurin and plastocyanin . . . ." and cites *Fiddes* as authority for unpatentability of a class due to lack of written description. Office Action, page 5. Claims in *Fiddes* to a "DNA molecule consisting essentially of a DNA sequence encoding mammalian basic fibroblast growth factor [FGF]" were unpatentable due to lack of written description. *Fiddes v. Baird,* 30 USPQ2d 1481, 1483 (BPAI, 1993). The patent in *Fiddes* claimed DNA to the broad class of mammalian FGFs, but taught only the amino acid sequence for bovine pituitary FGF. *Id.* No FGF DNA was taught in the patent, but for a theoretical sequence based on the amino acid sequence. *Id.*

The claims of *Fiddes* are distinguished from those of the present invention in that the Applicants provide written description of claimed azurin and plastocyanin sequences. See SEQ ID NOS: 1 and 2, respectively. Moreover, the amino acid sequences for the claimed cupredoxin sequences are provided, with written description as to how to create these sequences (Paragraphs [0112-0120];Fig. 11; Example 19, paragraph [0159], page 47 *et seq.*) and how to screen for their cytotoxic functionality (Example 20, paragraph [0167], page 50 *et seq.*). Finally, evidence for the cytotoxic activity of the sequences is presented in Fig. 12(b).

The Examiner argues further that "the specification does not teach *in vivo* administering a patient with any mutant or variant of any species of cupredoxin including azurin and plastocyanin." Office Action, p. 6. However, this statement is not applying the correct standard. The specification does <u>not</u> need to teach *in vivo* administering for every

compound claimed. All that is required is to establish that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *In re Kaslow* at 1375. Moreover, the specification teaches how to develop mutants, (Example 19), how to use these mutants for *in vitro* assays (Examples 20 and 21) and that a mutant can be used for treatment of cancer. Paragraph [0010]. Furthermore, the specification teaches in Examples 15, 16 and 18, how to administer cupredoxins to a patient *in vivo*. Because the specification teaches how to make the claimed cupredoxins and how to administer the cupredoxins of the present invention to a patient for treatment, one skilled in the art must reasonably conclude that the inventor had possession of the claimed invention.

The Examiner argues that the applicant does not provide any working examples. Office Action pgs 6-7. Again, the Examiner's argument is contradictory to the established law. The Applicant is not required to provide any working example in the specification. "A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language." *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (quoting *Lizardtech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005)). Only enough must be included to convince a person of skill in the art that the inventor possessed the invention. *Id.* Hence, lack of providing exact examples is not required. Hence, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 5, 6 and 10 under 35 U.S.C. § 112, first paragraph.

Enablement

Claims 1-10 and 20 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Office Action, p. 7. Applicants respectfully traverse

The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be

relied on for enabling support. *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.*

While not acquiescing to propriety of the grounds of this rejection, and solely in an effort to expedite prosecution,claims 1 and 2 have been amended to delete the language "or a functional variant or derivative thereof." Applicants reserve the right to file divisional and continuing applications with claims addressing the deleted subject matter. Applicants maintain that the claims as amended are fully supported by the specification.

The Examiner alleges that the specification "fails to provide objective evidence, which azurin or plastocyanin . . . binds to p53 to promote cell death." Office Action, p. 8. Applicants submit that the specification does indeed teach the induction of cell death, specifically via apoptosis, in the binding of cupredoxins to p53. Paragraph [081] teaches that "[a]zurin forms a complex with p53, stabilizes it. . . thereby inducing apoptosis. Further, whether mutant azurin proteins exhibit cytotoxic activity depends on whether there is continued ability of the mutant to form p53 complexes. See paragraphs [083]-[086]. After teaching the association of cytotoxicity with cupredoxin binding to p53, Applicants demonstrate this fact in Example 17, wherein cells lacking expression of p53 (i.e., cells of a p53(-/-) breast cell line) required twice as much azurin to achieve a level of cell death commensurate with that of the cells fully expressing p53 (i.e., cells of a p53(+/+) breast cell line), in the same amount of time. See paragraphs [0149]-[0151].

While not acquiescing to propriety of the grounds of this rejection, and solely in an effort to expedite prosecution, claim 5 has been amended to delete the language "or an amino acid sequence having at least 90% sequence identity with SEQ ID NO: 1. Claim 6 has been amended to delete the language "is an azurin comprising the amino acid sequence of SEQ ID NO:1, or an amino acid sequence having at least 90% sequence identity with SEQ ID NO:1 and wherein the cupredoxin." Claim 10 has been amended to delete the language "or an amino acid sequence having at least 90% sequence identity with SEQ ID NO: 2" and to add the language "a mutant plastocyanin or a truncated plastocyanin." Applicants reserve the right to file divisional and continuing applications with claims addressing the deleted subject

matter. Applicants maintain that the claims as amended are fully supported by the specification.

Support for the claimed cupredoxins is provided throughout the present application, e g., at paragraphs [014], [026], [027], [028], [078], [083-086], [0112-0120] and Examples 19-21 and Figures 11-13. See also U. S. Patent No. 7,089,105 (Ser. No. 10/047,710, filed January 15, 2002 from which the present application claims priority) which is coextensive with the present application and specifically discloses and claims truncated cupredoxins. As taught in paragraph [0112], mutations and/or truncations of cytotoxic factors can produce cytotoxic agents of varying compositions also demonstrating functional activity. Paragraphs [0112 -00120] teach how to develop a mutant cupredoxin such as azurin or plastocyanin. Moreover, Examples 19-21 and Figures 11-13 teach that mutant cupredoxins do induce the apoptosis rate and cell cytotoxicity.

The Examiner argues that the present specification is not enabling because the specification does not provide an *in vivo* example using variants of azurin, or variants of any other claimed cupredoxin. Office Action, pgs 8-9. However, "lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement." MPEP 2164.02. Moreover, the specification teaches how to use mutants for treating patients based on the *in vitro* result. For example, the specification teaches *in vivo* treatment with azurin in Examples 15, 16 and 18 and Figures 6 , 8 and 10. The specification also teaches comparison studies between azurin and its mutants *in vitro*. (Examples 20 and 21 and Figures 12 and 13). The specification therefore provides a standard and guidelines to enable one skilled in the art to view the comparative *in vitro* studies and the wt azurin *in vivo* studies, and extrapolate the amounts necessary for *in vivo* treatment using the claimed mutants or truncations. Since *in vivo* experiments have been taught AND *in vitro* experiments have been performed that establish a relative biological activity between wt cuproxins and its mutants, no undue experimentation would be required by one skilled in the art.

Moreover, establishing dosages *in vivo* for the claimed cupredoxins or its truncations or mutants is not undue experimentation for one skilled in the art. As determined in *Ex parte Skubulla*, while some experimentation may be required to determine optimum dosages for derivatives in order to achieve a particular biological response, such experimentation is not considered undue. *Ex parte Skubulla* 12 USPQ2d 1570 (Bd. Pat. App. & Inter. 1989).

The Examiner also argues that there is no example of a correlation between *in vitro* function and *in vivo* treatment. Office Action p. 9. When arguing a lack of correlation, the initial burden is on the Examiner to provide reasons or examples for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. MPEP 2164.02. The Examiner argues that an *in vitro* assay is unpredictable in correlating *in vivo* assays. Office Action p. 9. However, the Examiner, who has the burden, provides no reason for that statement. The Examiner provides three examples of unpredictability of biological variants. Office Action p. 8. However, the examples provided are irrelevant to the Examiner's argument that *in vitro* results are not sufficiently predictive for *in vivo* results. The Examiner, therefore, provides no support, legally or scientifically, to make such a rejection.

In contrast, the present application does provide examples of why *in vitro* results are predictive of *in vivo* results. For example, Example 17 and Figure 9 teach that azurin induces apoptosis of cancer cells *in vitro*. A subsequent *in vivo* study performed in mice, (Example 18 and Figure 10) shows a similar effect of the *in vitro* result, where the azurin treated tumor is significantly reduced relative to the control. Hence, in regard to the claimed cupredoxins, the specification does teach that *in vitro* results are predictive of *in vivo* results.

Moreover, the Examiner's argument that the result of *in vitro* treatment is unpredictable is contradictory to the established case law, under similar facts: "*In vitro* results with respect to the particular pharmacological activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation there between." *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985). Hence, the Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-10 and 20 under 35 U.S.C. § 112.

Double Patenting

Claims 1, 3 and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting, as allegedly being unpatentable over claims 18, 20 and 21 of co-pending Application No. 11/435,592. Office Action, page 10. Applicant respectfully traverses.

The Examiner has instructed that a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting ground. Without acquiescing to propriety of the grounds addressing the propriety of the Examiner's rejection, and specifically the Examiner's interpretation of what

the cited references teach or suggest, Applicants respectfully and properly defer addressing the present rejection until there is allowable subject matter in the present application. At that time, a terminal disclaimer will be filed if warranted by the Examiner's rejection in view of the allowed claims.

III. Rejection under 35 U.S.C. § 102(a)

Claims 1-2, and 20 are rejected under 35 U.S.C. § 102(a) as being anticipated by Yamada et al., (PNAS, vol 99, Page 14098-14103, Oct. 2002). Office Action, page 11. Applicants respectfully traverse.

Yamada et al., is not prior art to the present application. The present application claims priority to and is a continuation-in-part of U.S. Patent Application Serial Number 10/047,710, filed January 15, 2002, which claims priority to U.S. Provisional Application Serial Number 60/269,133, filed February 15th, 2001. As set forth above at pages 6-7, there is complete support for the subject claims in the priority applications. Hence, the Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2 and 20 under 35 U.S.C. § 102(a).

IV. Double patenting

Claims 1-6 and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting, as allegedly being unpatentable over claims 1-3, 5 and 7-12 of U.S. patent No. 7084105 in view of Yamada et al., (PNAS, vol 99, pages 14098-14103, Oct. 2002, applicant's IDA A23) Office Action, p. 12. Applicants respectfully traverse.

The Examiner has instructed that a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting ground. While not acquiescing or addressing the propriety of the Examiner's rejection, and specifically the Examiner's interpretation of what the cited references teach or suggest, Applicants respectfully and properly defer addressing the present rejection until there is allowable subject matter in the present application. At that time, a terminal disclaimer will be filed if warranted by the Examiner's rejection in view of the allowed claims.

Conclusion

Applicants have properly and fully addressed each of the Examiner's grounds for rejection. Applicants submit that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account.

Respectfully Submitted,

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